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EXAMINER

SAKELARIS, SALLY A

ART UNIT PAPER NUMBER

1634

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/904,968

Applicant(s)

GERMINO ET AL.

Examiner

Sally A Sakelaris

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 24 October 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-66 and 68-75 is/are pending in the application.
- 4a) Of the above claim(s) 18,30, 58 and 67 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-66 and 68-75 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4IDSs.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: TPages Alignments of SEQs.

## **DETAILED ACTION**

### ***Response to Arguments***

#### ***Election/Restrictions***

Applicant's arguments filed 11/26/02, 3/11/2003, and 10/24/2003 have been fully considered but they are not persuasive. Applicant's election with traverse of Group I, claims 1-66 as filed as well as newly added claims 68-75 as they are drawn to the primer pair of SEQ ID NOS: 3 and 4 and the nested primer pair of SEQ ID NOS: 19 and 20 which amplify the elected nucleic acid residue located at position 3336(Deletion) has been acknowledged. It should be noted that, while applicant in their response received 10/24/2003 on page 2 asserted that their elected nucleotide was that "mutation wherein nucleotide 3666"(Line 17), in light of the previous two non-responsive notices issued from the office and in order to allow prosecution to get underway, the examiner assumes that the applicant meant to elect "a position corresponding to nucleotide 3336, wherein nucleotide 3336 is deleted". The SEQ ID NOS: that were not elected, and claims directed to non-elected subject matter will not be examined as they are considered to be withdrawn until the time of allowance when rejoinder is possible, if warranted. Specifically, claims 18, 30, 58 and 67 are drawn to non-elected subject matter and are considered to be withdrawn. The traversal is on the ground(s) that the examiner's analysis has become tautological. Furthermore the applicant asserts that the different SEQ ID NOS; of their claims could be searched without a burden to the examiner. While the examiner acknowledges the applicants arguments, they are reminded that each of their claimed SEQ ID NOS: is patentably distinct in its structure and in its function. Additionally, a search of each and every SEQ ID NO: within the claims would in fact

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represent a burden on the office as the applicant has been afforded the opportunity "to include up to 10 nucleotide sequences per application" as instructed by the *Official Gazette* and notices posted on the PTO website.

The examiner retains his/her discretion in the inclusion of "up to 10 sequences." It is further maintained that the examiner adhered to the PTO policy concerning restriction practice as defined in 35 U.S.C. 121, "if two or more independent and distinct inventions are claimed in one application, the commissioner may require the application to be restricted to one of the inventions." The examiner maintains that the inventions are distinct, each from the other because of the following reasons:

These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequences are presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 et seq. Each primer sequence and nucleotide residue are patentably distinct because they are unrelated sequences, i.e. these sequences are unrelated because each has a different nucleotide composition and as a result different physical and biochemical properties and differs in structure and in function and in biological activity, while primers do not encode proteins, their ability to hybridize and subsequently prime amplification is a direct effect of their characteristic nucleic acid arrangement. The Examiner reaffirms that the groups are properly separated as their inclusive products are comprised by different nucleic acid sequences and as a result, create distinct groups with variant structural and functional capacities. The examiner maintains the restriction requirement

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made previously, as each group is correctly separated as unrelated or patentably distinct and as such make the requirement final.

### ***Priority***

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. The present application's claim to benefit of a U.S. provisional Application 60/218,261 filed July 13, 2000, and 60/283,691 filed 4/31/2001 are both granted.

### ***Claim Interpretations***

It should be noted that the claim language of "5' region" will be interpreted as at least including the single most 5' nucleotide and in the broadest sense as including every nucleotide but the most 3' nucleotide. Likewise, "3' region" will be interpreted as at least including the single most 3' nucleotide, and in the broadest sense as including every nucleotide except the most 5' nucleotide.

Furthermore, it should be noted that the claim language including "selectively hybridize" is interpreted as being able to hybridize under any sort of stringency conditions.

Also, recitations of "about", "at least about", "about 50" etc. will be interpreted liberally as an exact definition of these terms in the specification could not be located (See also 112 2<sup>nd</sup> rejection below).

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1-7, 20-22, 25, 31, 37-39, 43-44, 46-49, 59, and 62 are rejected under 35 U.S.C. 102(b) as being anticipated by Klinger et al.(US Patent 5,654,170).

With regard to claim 1, Klinger et al. teach a primer comprising a 5' region and adjacent 3' region, said region comprising a nucleotide sequence that selectively hybridizes to a PKD1 gene sequence and, optionally, to a PKD1 gene homolog sequence, and said 3' region comprising a nucleotide sequence that selectively hybridizes to a PKD1 gene sequence, and not to a PKD1 gene homolog sequence, provided the primer does not consist of a sequence as set forth in SEQ ID NO:11, 18, 52, and 60(Abstract, Col. 5 lines 45-67 – Col. 6 1-4 and figure 3B).

With regard to claims 2-4, Klinger teaches the above primer wherein said 5' region comprises at least about ten contiguous nucleotides, wherein the 3' region comprises at least one 3' terminal nucleotide identical to a nucleotide that is 5' and adjacent to the nucleotide sequence of the PKD1 gene to which the 5' region of the primer can hybridize, and wherein said 3' terminal nucleotide is different from a nucleotide that is 5' and adjacent to a nucleotide sequence of the PKD1 homolog to which the 5' region of the primer can hybridize wherein the 3' region comprises about 2 to 4 3' terminal nucleotides and a 5' region of about 14 to 18 nucleotides and a 3' region of about 2 to 6 nucleotides in their teaching of the primer in Figure 3B of 5'AGGACCTGTCCAGGCATC 3'.

With regard to claims 5-7, Klinger teaches in Col. 5, that the "present invention encompasses isolated oligonucleotides corresponding to sequences within the PKD1 gene

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and PKD1cDNA, which, alone or together, can be used to discriminate between the authentic expressed PKD1 gene and PKD1 homologues or other repeated sequences. These oligonucleotides may be from about 12 to about 60 nucleotides in length, preferably about 18 nucleotides; may be single or double stranded, and may be labeled or modified as described below. An example of an oligonucleotide that can be used in this manner is shown in Fig. 3B”(Col. 5). (Note: art has been applied according to the specification’s definition of “substantially identical” on page 21, a primer with “at least about 80% identity to one of SEQ ID NOS: 3 to 51 and 61 to 113”)

With regard to claim 20, 59, and 62, Klinger et al. teach an isolated polynucleotide, comprising a contiguous sequence of at least about ten nucleotides substantially identical to a nucleotide sequence of SEQ ID NO:1 or to a nucleotide sequence complementary thereto, the contiguous nucleotide sequence comprising a position corresponding to nucleotide 3336, wherein nucleotide 3336 is deleted(Col. 5 lines 45-67 and Col. 6 lines1-17). Furthermore, the reference teaches that “deletions may be detected using a PCR-based assay , in which pairs of oligonucleotides are used to prime amplification reactions and the sizes of the amplification products are compared with those of control products”(Col. 8 lines 36-40).

With regard to claims 21 and 22, Klinger et al. teach the above polynucleotides in a vector and furthermore the host cell transformed by this vector. The abstract teaches that “the invention also encompasses vectors comprising these nucleic acids, host cells transformed with the vectors”( + Col. 6 lines 39-67 and Col. 7 lines 1-15).

With regard to claim 25 and 43, Klinger et al. teach a method of detecting the presence or absence of a mutation in a PKD1 polynucleotide in a sample, the method

comprising: contacting nucleic acid molecules in a sample with at least one primer pair of claim 7 under conditions suitable for amplification of a PKD1 polynucleotide by the primer pair, thereby generating a PKD1-specific amplification product, under said conditions; and identifying the presence or absence of a mutation in the PKD1-specific amplification product, thereby detecting the presence or absence of a mutation in the PKD1 polynucleotide in the sample(See for example Col. 8 lines 35-60 and Col. 9 lines 47-67 and Col. 10 lines 1-40).

With regard to claim 31, Klinger et al. further teach the above method of identifying the presence or absence of a mutation in the amplification product comprises determining the nucleotide sequence of the amplification product as taught in the embodiment of the assay used to detect the presence of mutation in Col. 10 for example of "direct DNA sequencing" line 35(+ Col. 8 lines 35-38).

With regard to claim 37, 44 and 49 Klinger et al. teach the method of detecting a presence or the absence of a mutation wherein a primer extension assay is used and performed with a detectably labeled primer(Col. 5 line 52) and a mixture of deoxynucleotides and dideoxynucleotides(sequencing and also see Col. 14 lines 1-10), and wherein the primer are selected so as to enable differential extension of the primer in the presence of a wild-type PKD1 polynucleotide as compared to a mutant PKD1 polynucleotide. Although the sequencing method taught by the reference(Col. 10 line 35) teaches the limitation of claim 37, the PCR reaction of Cols 13 and 14 also anticipate the limitation of 37 and 44 in their use of a sample from a subject("whole blood samples" Col. 12 line 63) to obtain their data.



With regard to claims 38, 39, and 48 Klinger teaches that the above method is performed both using a plurality of primer pairs and in a high throughput format utilizing a plurality of samples(Col. 11, lines 11-17).

With regard to claims 46-47 wherein identifying the presence or absence of a mutation in the amplification product is associated with the PKD1-associated disorder autosomal dominant polycystic kidney disease(Col. 1 lines 10-49).

2. Claims 16-17, 19, 40 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by of Brennan (US Patent 5,474,796).

Brennan teaches an array having thereon every possible 10 mer nucleic acid. This array inherently comprises all of the plurality of primer sequences capable of hybridizing to PKD1. Thus, every possible primer for every possible ten-mer subsequence of any one of instant primers of PKD1 is comprised on the array taught by Brennan. Therefore, Brennan anticipates the instantly claimed invention.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of

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each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 8-15, 26, 28, 29, 54, 68-72, and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Buck et al (Biotechniques (1999) 27(3):528-536).

With regard to claim 1, Klinger et al. teach a primer comprising a 5' region and adjacent 3' region, said region comprising a nucleotide sequence that selectively hybridizes to a PKD1 gene sequence and, optionally, to a PKD1 gene homolog sequence, and said 3' region comprising a nucleotide sequence that selectively hybridizes to a PKD1 gene sequence, and not to a PKD1 gene homolog sequence, provided the primer does not consist of a sequence as set forth in SEQ ID NO:11, 18, 52, and 60(Abstract, Col. 5 lines 45-67 – Col. 6 1-4 and figure 3B).

With regard to claims 2-4, Klinger teaches the above primer wherein said 5' region comprises at least about ten contiguous nucleotides, wherein the 3' region comprises at least one 3' terminal nucleotide identical to a nucleotide that is 5' and adjacent to the nucleotide sequence of the PKD1 gene to which the 5' region of the primer can hybridize, and wherein said 3' terminal nucleotide is different from a nucleotide that is 5' and adjacent to a nucleotide sequence of the PKD1 homolog to which the 5' region of the primer can hybridize wherein the 3' region comprises about 2 to 4 3' terminal nucleotides and a 5' region of about 14 to 18 nucleotides and a 3' region of about 2 to 6 nucleotides in their teaching of the primer in Figure 3B of 5'AGGACCTGTCCAGGCATC 3'.

With regard to claims 5-7, Klinger teaches in Col. 5, that the “present invention encompasses isolated oligonucleotides corresponding to sequences within the PKD1 gene and PKD1cDNA, which, alone or together, can be used to discriminate between the authentic expressed PKD1 gene and PKD1 homologues or other repeated sequences. These oligonucleotides may be from about 12 to about 60 nucleotides in length, preferably about 18 nucleotides; may be single or double stranded, and may be labeled or modified as described below. An example of an oligonucleotide that can be used in this manner is shown in Fig. 3B”(Col. 5). (Note: art has been applied according to the specification’s definition of “substantially identical” on page 21, a primer with “at least about 80% identity to one of SEQ ID NOS: 3 to 51 and 61 to 113”)

With regard to claim 20, 59, and 62, Klinger et al. teach an isolated polynucleotide, comprising a contiguous sequence of at least about ten nucleotides substantially identical to a nucleotide sequence of SEQ ID NO:1 or to a nucleotide sequence complementary thereto, the contiguous nucleotide sequence comprising a position corresponding to nucleotide 3336, wherein nucleotide 3336 is deleted(Col. 5 lines 45-67 and Col. 6 lines 1-17). Furthermore, the reference teaches that “deletions may be detected using a PCR-based assay , in which pairs of oligonucleotides are used to prime amplification reactions and the sizes of the amplification products are compared with those of control products”(Col. 8 lines 36-40).

With regard to claims 21 and 22, Klinger et al. teach the above polynucleotides in a vector and furthermore the host cell transformed by this vector. The abstract teaches that “the invention also encompasses vectors comprising these nucleic acids, host cells transformed with the vectors”(Col. 6 lines 39-67 and Col. 7 lines 1-15).

With regard to claim 25 and 43, Klinger et al. teach a method of detecting the presence or absence of a mutation in a PKD1 polynucleotide in a sample, the method comprising: contacting nucleic acid molecules in a sample with at least one primer pair of claim 7 under conditions suitable for amplification of a PKD1 polynucleotide by the primer pair, thereby generating a PKD1-specific amplification product, under said conditions; and identifying the presence or absence of a mutation in the PKD1-specific amplification product, thereby detecting the presence or absence of a mutation in the PKD1 polynucleotide in the sample(See for example Col. 8 lines 35-60 and Col. 9 lines 47-67 and Col. 10 lines 1-40).

With regard to claim 31, Klinger et al. further teach the above method of identifying the presence or absence of a mutation in the amplification product comprises determining the nucleotide sequence of the amplification product as taught in the embodiment of the assay used to detect the presence of mutation in Col. 10 for example of "direct DNA sequencing" line 35(+ Col. 8 lines 35-38).

With regard to claim 37, 44 and 49 Klinger et al. teach the method of detecting a presence or the absence of a mutation wherein a primer extension assay is used and performed with a detectably labeled primer(Col. 5 line 52) and a mixture of deoxynucleotides and dideoxynucleotides(sequencing and also see Col. 14 lines 1-10), and wherein the primer are selected so as to enable differential extension of the primer in the presence of a wild-type PKD1 polynucleotide as compared to a mutant PKD1 polynucleotide. Although the sequencing method taught by the reference(Col. 10 line 35) teaches the limitation of claim 37, the PCR reaction of Cols 13 and 14 also anticipate the

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limitation of 37 and 44 in their use of a sample from a subject(“whole blood samples” Col. 12 line 63) to obtain their data.

With regard to claims 38, 39, and 48 Klinger teaches that the above method is performed both using a plurality of primer pairs and in a high throughput format utilizing a plurality of samples(Col. 11, lines 11-17).

With regard to claims 46-47 wherein identifying the presence or absence of a mutation in the amplification product is associated with the PKD1-associated disorder autosomal dominant polycystic kidney disease(Col. 1 lines 10-49).

With regard to Claims 8-15, 26, 28, 29, 54, 68-72, and 74, Klinger et al. teach SEQ ID NO:1, which includes all of the SEQ ID NOS of 3, 4, 19 and 20(See attached alignments). While Klinger et al. define their 31,571 base pair sequence as the PKD1 genomic sequence and furthermore teach the “isolated oligonucleotides corresponding to sequences within the PKD1 gene or within the PKD1 cDNA, which alone or together, can be used to discriminate between the authentic expressed PKD1 gene and PKD1 homologues or other repeated sequences”(Col. 5, lines 40-55) and also “an example of an oligonucleotide that can be used in this manner(See Fig. 3B); Klinger does not teach the primer sequences of SEQ ID NOS of 3, 4, 19 and 20, only the sequences in the genomic form of their SEQ ID NO:1(see alignments).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have selected the primers of SEQ ID NOS: 3, 4, 19 and 20 from the Klinger’s known sequence of SEQ ID NO: 1 for the expected benefit of obtaining functionally equivalent primers with the ability to “selectively prevent the

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amplification of PKD1 homologue sequences. In this manner authentic PKD1 sequences are selectively amplified”(Col. 5 lines 64-67)

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious.

Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of PDK1, and in particular for the detection of the authentic sequence of PDK1 not homologs, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page

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533, column 1). Buck expressly states “The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2).” Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

4. Claims 27, 53, 55, 60, 61, 73, and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Buck et al (Biotechniques (1999) 27(3):528-536) and further in view of Shapira et al.(PNAS 1991)

While the teachings of Klinger et al. in view of Buck et al. can be read above, the two references do not teach the limitation of claims 27, 53, 55, 60, 61, 73, and 75 that includes the nesting of primer pairs one inside the other.

However, Shapira et al. teach a method of amplifying nucleic acids by way of nested primer pairs. The reference teaches that following a first round of PCR, “a second round of PCR utilizing the nested primers in Fig. 2 in a reaction mixture containing the same concentrations of all of the above constituents, except for 1.5 mM MgCl<sub>2</sub> and a 5ul aliquot of the previous PCR reaction mixture that served as the DNA template”(Pg. 7529 left).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the nesting of primer pairs teachings of Shapira with nested the SEQ ID NOS: 3, 4, 19 and 20 as taught by Klinger et al in view

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of Buck for the expected benefit that “nested-primer PCR provided the sensitivity to analyze...that was not available with Southern blotting techniques”(Pg. 7528 right).

5. Claims 32-33 and 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Buck et al (Biotechniques (1999) 27(3):528-536) and further in view of Sathe et al.(US Patent 6,362,326).

While the teachings of Klinger et al. in view of Buck et al. can be read above, the two references do not teach the limitation of claims 32-33 and 35-36 that include the use of temperature melting, HPLC, and SSCP analysis on the amplification products in order to identify the presence or absence of a mutation.

However, Sathe et al. teach the detection of mutations on the DNA level through “single-stranded conformation polymorphism assay (SSCA or SSCP)”(Col. 8 lines64-65). The references continues to teach that the “increased throughput possible with SSCA makes it an attractive, viable alternative to direct sequencing for mutation detection”(Col. 9 lines 1-10). Even further, “denaturing HPLC, similar to SSCP, can be used which uses a PCR amplified product, run down a heated HPLC column; the heating disassociates the DNA strands and one usually sees two peaks if there is a variation in allelic forms”(Col. 9 lines 14-18) “and it works on the same principles as SSCP”

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Sathe’s SSCA and HPLC in mutation detection to method and SEQ ID NOS: 3, 4, 19 and 20 as taught by Klinger et



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al in view of Buck for the expected benefit of these techniques being a “viable alternative to direct sequencing for mutation detection”(Col. 9 lines 1-10).

6. Claims 16-17, 19, 40 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Brennan (US Patent 5,474,796).

While the teachings of Klinger et al. can be read above, the reference does not teach the limitation of claims 16-19 and 40 and 42 that include the primers immobilization on a solid matrix such as a microchip or an array.

However, Brennan teaches an array having thereon every possible 10 mer nucleic acid. This array inherently comprises all of the plurality of primer sequences capable of hybridizing to PKD1. Thus, every possible primer for every possible ten-mer subsequence of any one of instant primers of PKD1 is comprised on the array taught by Brennan. Therefore, Brennan teaches the instantly claimed invention.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Klinger’s method and primer and practiced them on the solid support of Brennan for the expected benefit of “producing large, dense arrays of solid phase bound reactants in a reproducible and rapid manner”(Col. 2 lines 5-7) as current methods “do not conveniently and reliably produce the very large, high density arrays”.

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7. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Brennan (US Patent 5,474,796) and in further view of Brennan (US Patent 5,472,672).

While the teachings of Klinger et al. in view of the first Brennan can be read above, the reference does not teach the limitation of claim 41 that includes the limitation of the immobilization of primers on a solid matrix such as a microtiter plate.

However, Brennan (US Patent 5,472,672), teaches in Col. 6 lines 9-10 that “in a preferred embodiment, an array of wells 26 (Fig.1) is provided formed in a microtiter plate...the synthesiseis apparatus is particularly configured to employ a 96-well microtiter plate”(Col. 6). Therefore, Brennan teaches the instantly claimed invention.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Klinger’s method and primer and practiced them on the solid support of Brennan for the expected benefit of “producing large, dense arrays of solid phase bound reactants in a reproducible and rapid manner”(Col. 2 lines 5-7) as current methods “do not conveniently and reliably produce the very large, high density arrays” and further obvious to have also used microtiter plates in the same format as current methods “do not conveniently and reliably mass produce very large arrays necessary for effective large scale sequencing”(Col. 3 lines 23-25).

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8. Claims 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Iliff (US Patent 6,234,964).

While the teachings of Klinger can be seen above, the reference does not teach the limitations of claims 50-52 including transmitting a report to a user via internet, fax or mail.

However, Iliff teach a disease management system that “gives the patient the option of receiving a summary of the consultation session and specific recommendations provided by the system via facsimile, electronic mail, or mail service”(Col. 12 lines30-67).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Klinger’s method and primer and transmitted their resulting data through a report to a user using a fax, e-mail, or regular mail of Iliff for the expected benefit of “promoting patient health in an automated manner that reduces costly medical intervention”(Abstract).

9. Claims 55-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Buck et al (Biotechniques (1999) 27(3):528-536) and further in view of Shapira et al.(PNAS 1991) in further view of Sathe et al.(US Patent 6,362,326).

While the teachings of Klinger et al. in view of Buck et al. and in a further view of Shapira et al. can be read above, but the three references do not teach the limitation of claims 55-57 of temperature melting, HPLC, and SSCP analysis on the amplification products in order to identify the presence or absence of a mutation.

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However, Sathe et al. teach the detection of mutations on the DNA level through “single-stranded conformation polymorphism assay (SSCA or SSCP)”(Col. 8 lines 64-65). The references continues to teach that the “increased throughput possible with SSCA makes it an attractive, viable alternative to direct sequencing for mutation detection”(Col. 9 lines 1-10). Even further, “denaturing HPLC, similar to SSCP, can be used which uses a PCR amplified product, run down a heated HPLC column; the heating disassociates the DNA strands and one usually sees two peaks if there is a variation in allelic forms”(Col. 9 lines 14-18) “and it works on the same principles as SSCP”

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Sathe’s SSCA and HPLC in mutation detection to the nested primer pair method and SEQ ID NOS: 3, 4, 19 and 20 as taught by Klinger et al in view of Buck and in further view of Shapira for the expected benefit of these techniques being a “viable alternative to direct sequencing for mutation detection”(Col. 9 lines 1-10).

10. Claims 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Ahern et al.(The Scientist, 1995)

While the teachings of Klinger et al are summarized above, the reference does not teach a kit for detecting the presence or absence of a mutation in a PKD1 gene,

However, Ahern teaches that “biochemical, reagents kits offer scientists good return on investment” as combining the reagents into a kit form offers scientists “the opportunity to better manage their time, putting these products all together in kits takes the convenience one step further”(Pg. 4 top).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Klinger’s primers and methods into a kit taught by Ahern for the expected benefit of “buying premade reagents and kits because they are convenient and they save time”(Pg. 4).

11. Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Buck et al (Biotechniques (1999) 27(3):528-536) and further in view of Koster et al.(US Patent 6,225,450).

While the teachings of Klinger et al. in view of Buck et al. can be read above, the two references do not teach the limitation of claim 34 that includes the use of matrix-assisted laser desorption time of flight mass spectrometry on the amplification products in order to identify the presence or absence of a mutation.

However, Koster et al. teach a method of “DNA sequencing that utilizes the sanger sequencing strategy and assembles the sequence information by analysis of the nested fragments obtained by base-specific chain termination via their different molecular masses using mass spectrometry as for example Maldi(Abstract)” The reference further

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teaches that "MALDI can be particularly attractive when a time of flight (TOF) configuration is used as a mass analyzer"(Col. 6 lines 45-47).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Koster's MALDI TOF method and SEQ ID NOS: 3, 4, 19 and 20 as taught by Klinger et al in view of Buck for the expected benefit of these techniques providing a "high speed, high throughput, no electrophoresis and gel reading artifacts...and no costly reagents involving various substitutions with stable isotopes"(Abstract).

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-17, 19-57, 59-66 and 68-75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-17, 19-45, 47-57, 59-66 and 68-75 are indefinite over the recitation of "PKD1" as it is unclear to which "PKD1" they are referring. Without reading limitations of the specification into the claims, it is not clear if PKD1 is meant to refer to "polycystic kidney disease gene" or alternatively a gene sequence of the pKD1 plasmid of *Kluyveromyces drosophilarum*(See US Patent 5,166,070 as an example). Appropriate clarification is required.

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B. Claims 2-4, 20-24, 62, and 66 are indefinite over the phrase "at least about". It is vague and indefinite what is meant by the phrase "at least about 10 contiguous nucleotides". The phrase "at least" typically indicates a minimum point. The phrase "at least" however, is contraverted by the term "about" which implies that values above and below 10 nucleotides are permitted. Further, the extent of variance permitted by "about" is unclear in this context. Since nucleotides are whole numbers, "about 10" cannot mean from 8.4 to 11.6 because nucleotides cannot be split in half. Therefore, it is also unclear if "about 10" simply includes 7 or if it also includes 1-8 as well. In Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200 (CAFC 1991), the CAFC stated, "The district court held claims 4 and 6 of the patent invalid because their specific activity limitation of "at least about 160,000" was indefinite". After review, the CAFC states "We therefore affirm the district court's determination on this issue." Thus, the CAFC found the phrase "at least about" indefinite where the metes and bounds of the term were not defined in the specification.

***35 U.S.C. 112, Written Description Rejection***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-66 and 68-75 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention

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The specification discloses SEQ ID NO: 1 which the specification asserts corresponds to the wt PKD1 gene (pg. 26). Claims 1-66 and 68-75 are directed to encompass sequences comprising nucleotides that selectively hybridize to a PKD1 gene sequence and optionally to a PKD1 homolog sequence, primers comprising regions wherein at least 10 contiguous nucleotides that "can hybridize", primers comprising regions which "can selectively hybridize to a nucleotide sequence flanking and within about fifty nucleotides", primers comprising a nucleotide sequence substantially identical to any of SEQ ID NOS 3, 4, 19, or 20, primers which can amplify a portion of SEQ ID NO:1 comprising about nucleotides 2043 to 4209, etc. For example, claim 7 as written could encompass any T3 and T7 primer pair that "can amplify" a cloned region of SEQ ID NO:1 comprising about nt 2043 to 4209. Thus, the instant claims encompass nucleic acids and methods that comprise any number of potential sequences when one considers that they encompass nucleic acids that comprise partial matches to the recited SEQ ID numbers and the ability to "hybridize" to and "can amplify" even more sequences. This genus can read on any number of possible primers comprising any number of known and unknown nucleic acid fragments, yet the specification has only disclosed the nucleic acids of SEQ ID NO: 1 and primers of SEQ ID NOS: 3, 4, 19, and 20. A review of the full content of the specification indicates that the sequence of nucleotides of SEQ ID NO: 1 and all aforementioned variations, are essential to the operation and function of the claimed invention. None of these sequences meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO: 1, 3, 4, 19 and 20, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides regardless of



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the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." *Id.* at 1170, 25 USPQ2d at 1606.

The named ORF is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for isolating and characterizing cDNA sequences from *E. grandis*, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe *E. grandis* cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the specification does, does not necessarily describe

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the cDNA itself. No sequence information indicating which nucleotides constitute *E. grandis* cDNA appears in the application. Accordingly, the specification does not provide a written description of the invention of claims 1, 4, and 6-15.

Therefore, none of the sequences encompassed by the claim meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (571)272-0748. The examiner can normally be reached on Monday-Thursday from 7:30AM-5:00PM and Friday from 1:00PM-5:00PM.

If attempts to reach the examiner are unsuccessful, the primary examiner in charge of the prosecution of this case, Jeffrey Fredman, can be reached at (571)272-0742. If attempts to reach the examiners are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)272-0782. The official fax number is (703)872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (571)272-0518.

Sally Sakelaris

  
1/26/2004

  
JEFFREY FREDMAN  
PRIMARY EXAMINER